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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/756,818	01/13/2004	Stephen James Russell	07039-416002	2374

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EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/756,818	RUSSELL ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/13/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 3/17/2005 is acknowledged. Claims 19-26 are pending in the instant application. The sections of title 35 U.S.C not included in this office action can be found in a previous office action. An action on the merits follows.

Claim Rejections - 35 USC § 112

Claims 19-26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising a) transfecting a cell with a nucleic acid sequence encoding a protein operably linked to a tetracycline regulatable promoter *in vitro*, and b) increasing expression of the protein using tetracycline *in vitro*, does not reasonably provide enablement for administering the cells to a mammal that has had an immune response against the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for reasons of record set forth in the previous office action of 12/01/2004. While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided.

Response to Arguments

Applicant's arguments filed 3/17/2005 have been fully considered but they are not persuasive. Applicants argue the claims do not require obtaining a therapeutic effect, or a gene

therapy "success story." Applicant's argument is not persuasive. The only disclosed purpose for such methods is for gene therapy (e.g. pg 2, line 12, "cancer therapy"; pg 3, lines 2 1-23, "leukocytes that elicit an anti- tumor effect" pg 8, line 24, "therapeutic (immunogenic) protein"; pg 20, therapeutic genes). Further, applicant argues that a person having ordinary skill in the art would have appreciated that one purpose of the claimed method is to provide a way for cells designed to express an immunogenic polypeptide to avoid a mammal's pre-existing response to that immunogenic polypeptide. This purpose was not asserted in the specification. Merely increasing expression of a protein in the absence of therapeutic effect does not have an art recognized use in a mammal with an immune response to the protein, prior to administration of the cell. Further applicant has not provided any supporting documentation indicating that this utility was established in the art at the time of filing.

Next Applicant argues that the relevance of the cited references regarding gene therapy is questionable. Specifically, applicant argues that the reference of "the Crystal was apparently cited for the notion that to enable the presently claimed invention, one must design the ideal vector." Applicant is invited to review pages 3 and 4 of the previous office action of 12/01/2004, wherein the examiner has cited multiple references that teach the problems and unpredictability of: 1) an *ex vivo* method of gene therapy to treat cancer (Ross et al); 2) the unpredictability of an *in vivo* method of gene therapy because of the unpredictability of gene delivery and expression *in vivo* (Verma et al); 3) the unpredictability of the combination of elements to obtain a therapeutic effect using gene therapy (Miller et al); 4) the problems of successful gene therapy are related to gene targeting and expression; and 5) the problems of designing gene transfer vectors that are efficient, specific and regulatable (Crystal et al). The problem is not the design or administration

of an ideal vector. The issues raised by the references cited by the examiner in the prior action relate to the unpredictability in the art of any method of gene therapy, such as cancer therapy, without providing a fully enabling disclosure. Applicant further argues that their specification discloses multiple drug-regulatable promoters, and that there is no need for high efficiency *in vivo* gene transfer or target specificity. This argument is not found to be persuasive since applicant has not provided any evidence indicating that the claimed method can be practiced in any mammal in order to achieve the stated utility of a therapeutic effect, in a method of cancer therapy. The specification only discloses the transfection of Jurkat cells with a vector encoding a chimeric T-cell receptor (TCR) operably linked to the tetracycline operator and encoding tTA. However, applicant has not provided any working examples describing the use of the claimed invention in any mammal. Nor has applicant provided any references or other support that would suggest that the examples provided in Jurkat cells enable provide full enablement of the claimed invention for use in any mammal.

Finally, applicant argues that no undue experimentation was required to practice the claimed invention since a person with ordinary skill in the art could obtain a cell with a vector containing a drug-regulatable promoter, such as a tetracycline regulatable promoter, operably linked to a nucleic acid encoding a peptide and they could have easily infused or injected the cells into a mammal's bloodstream. While these two steps may not require undue experimentation, applicant's invention has other requirements. First applicant must practice these steps in a mammal that has a prior immune response to said polypeptide. Next, as previously stated, the only asserted utility of the claimed method is to produce a therapeutic effect in the context of a method of cancer therapy. Given applicant's total lack of guidance on practicing the

claimed invention in any mammal, the skilled practitioner would not be able to predict how to achieve any therapeutic effect in a method of cancer therapy in any mammal.

Further, as stated in the prior office action, Miller et al. (May 1, 1997, Human Gene Therapy, Vol. 8, pages 803-815) teaches the gene regulation system that cap be applied to gene therapy in humans is yet unknown (page 809, column 2, line 42). Applicants do not demonstrate regulating any genes in humans or in any art recognized *in vivo* model. Without such guidance, the specification does not enable regulating the expression of a transgene in a mammal as claimed. In particular, the specification does not enable regulating the expression of a polypeptide by "altering the amount of regulatory drug" after the cell has been administered as encompassed by claim 19. The specification does not teach dosage, routes of administration or methods of targeting cells transfected with the polypeptide such that expression can be regulated after the cells have been introduced.

The claims are directed toward various regulatable systems including the tetracycline system. Miller et al. teaches that it is unpredictable which cells the tetracycline system may be applied to (page 809, column 2, 2nd 111 paragraph). Applicants demonstrate transfecting T-cells with a chimeric TCR under the control of a tetracycline system and controlling expression *in vitro* (page 29), but do not correlate the results obtained to other cell lines such that any cell line is enabled. Thus, if applicants intend to claim using the tetracycline regulatory system, the claims should be limited to T cells, which are enabled in the specification. Without adequate guidance as to which cells can be used to express proteins using the tetracycline regulatory system, it would require the skilled practitioner undue experimentation to determine which cells can be used with the tetracycline regulatory system.

The rejection of the claims is maintained for the reasons of record stated above and in the prior office action of 12/01/2004.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

The rejection of claims 19-26 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Response to Arguments

Applicant's arguments filed 3/17/2005 have been fully considered but they are not persuasive. Applicant argues that page 6, line 20 of the specification defines altering the amount of regulatory drug as increasing or decreasing the amount. However, this definition fails to limit the meaning of the term altering or otherwise provide guidance on the range of concentrations encompassed by the term altering. As previously stated, the term "altering" encompasses a range of changes from reducing the amount of drug administered to zero or raising it to near toxic levels. Therefore the metes and bounds of what the applicants mean by "altering the amount of regulatory drug" in step (c) cannot be determined.

Examiner's Comment

The closest prior art of record is exemplified by US Patent NO. 6,143,551 (11.7.2000). US Patent NO. 6,143,551 provides guidance on the administration of the introduction of a

nucleic acid sequence comprising a drug-inducible promoter to a cell for the production of polypeptides in a mammal. However, US Patent NO. 6,143,551 does not teach that the mammal has already made an immune response to said polypeptide.

Conclusion

The rejection of the claims is maintained for the reasons of record stated above and in the prior office action of 12/01/2004.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information

Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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